Quinolinic Acid's Modus Operandi

Several observations have suggested how excess levels of quinolinic acid might damage neurons. So far, however, these results are limited to in vitro studies, says Madeleine Price, professor of neurobiology and psychiatry at Washington University School of Medicine. The neurotoxin, which is known to bind to NMDA receptors, may overstimulate the neurons, says Price. This would open ion channels, flooding the neurons with sodium and water while disabling the ion pumps that maintain equilibrium. Alternatively, a delayed toxicity may result when quinolinic acid depolarizes the NMDA receptors, and calcium flows into the neurons. This activates proteases, which may somehow cause the damage. Melvin Heyes, a neuroscientist at the National Institute of Mental Health who developed a sensitive assay for quinolinic acid, believes that the neurotoxin may also interfere with cognitive processes by jamming the receptors without killing the neurons.

As for where the excess quinolinic acid comes from, Heyes argues that it is one end product of a six-step metabolic pathway that begins with the amino acid tryptophan. Normally the pathway is all but inactive, but Heyes suggests that gamma interferon, produced when the immune system is activated, turns on the enzyme indolamine 2,3-dioxygenase, which catalyzes the first step in the pathway.

Although Heyes' theory has yet to be proven, he argues that it would explain why, when HIV-infected patients take the drug AZT, quinolinic acid levels drop, and cognitive processes improve. AZT, Heyes points out, inhibits viral reproduction, and the drop in quinolinic acid may be a result of reduced immunological response.

–D.H.

invade the brain during inflammatory brain diseases, can produce more than enough quinolinic acid in vitro to account for levels of the compound that his assay has found in patients' cerebrospinal fluid. And in a paper published in the September *Journal of Neuroimmunology*, Heyes and Brew, now at the University of New South Wales in Sydney, report that the rise in quinolinic acid seems to be proportional to activation of the immune system. They argue that gamma interferon, which is released during immune stimulation, plays a key role in the metabolic pathway that converts the amino acid tryptophan to quinolinic acid (see box).

Schwarcz offers an alternative explanation. He has shown that astrocytes are the only source of quinolinic acid in normal brains. And since these cells play an important role in inflammatory processes as a target and source of cytokines, he argues that they may be a source of the quinolinic acid Heyes and his collaborators have detected. And Giulian, whose own research has failed to show quinolinic acid production by macrophages in culture, suggests that the neurotoxin may be produced in the liver and cross the blood-brain barrier.

Some researchers are also quick to point out that Heyes has not yet proven that quinolinic acid is the major cause of the neurological problems associated with inflammatory brain disease. Giulian argues, for example, that no excess quinolinic acid is found in some diseases, such as Alzheimer's, that involve chronic inflammation. Others, such as neurologist Richard Price of the University of Minnesota, who contributed the samples of cerebrospinal fluid from AIDS patients while at Memorial Sloan Kettering Cancer Center that Heyes assayed in his HIV study, suggest that other neurotoxins may be just as significant. Quinolinic acid, he says, is "probably not the only substance involved, and indeed, it remains to be seen whether it is the most important one." And Heyes collaborator John Halperin, chairman of the department of neurology at North Shore University Hospital in Manhasset, says that although a slight mental slowing down among mildly afflicted Lyme patients "correlates crudely" with a mild elevation of quinolinic acid, other compounds as yet unidentified could be involved in pathologies of severely afflicted patients.

Heyes responds that "they are absolutely right. The quinolinic acid finding has never implied that there are no other factors. But the burden of proof is on identifying those compounds, not on me to refute their hypothetical existence."

Although the hypothesis still remains to be proven, some researchers are intrigued by the potential for developing new therapies to control, treat, or reverse neurological impairments. NMDA receptor blocking compounds, which prevent the binding of quinolinic acid, have been developed, notes UCSF's Martin, and a few are already being tested by pharmaceutical companies. "The possibility of blocking this pathway with pharmaceutical agents is real and should be put to experimental tests, " he says.

–David Holzman

David Holzman is a Washington, D.C.-based science writer.

MATHEMATICS

If You Can't See It, Don't Believe It...

Looks can be deceptive—especially when what you're trying to picture exists not in the familiar world of planes or three-dimensional space but in the abstract realm of higher dimensions. There, where looks are limited to what the mind's eye can see, mathematicians have tended to set their compass by what they know is true in two- and three-dimensional space. Often enough, those intuitions are valid in higher dimensions as well. But not always.

Trying to generalize from plane and solid geometry to higher-dimensional space can get you into trouble, as Jeff Lagarias and Peter Shor at AT&T Bell Laboratories in Murray Hill, New Jersey, have shown by putting the kibosh on a proposal, known as Keller's conjecture, about the possible ways of filling space with n-dimensional building blocks. Likewise, Jeff Kahn at Rutgers University and Gil Kalai at the Hebrew University in Israel found higher-dimensional counterexamples to a statement known as Borsuk's conjecture, which sought to generalize the obvious fact that if you break a stick in two, both pieces are shorter than the original. Higher-dimensional spaces, it seems, aren't just amplified versions of the geometries we know well; they are strange lands with their own customs.

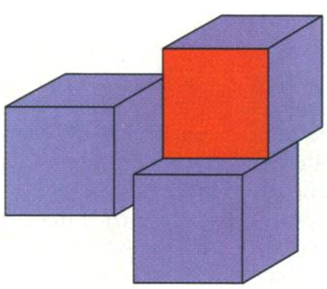
That bodes ill for other efforts to understand what life is like in higher dimensions by drawing analogies with the lower-dimensional spaces in which we are at home. The results show "we have very little intuition as to what's going on in high dimensions," Shor admits. The implications go beyond abstract mathematics, notes Joel Spencer, a mathematician at the Courant Institute in New York City. Higher-dimensional geometry may sound abstruse, but mathematicians venture into it whenever they wrestle with a problem involving many variables—and such problems abound in science, from modeling economic activity to analyzing DNA sequences. "Each dimension represents a variable," Spencer explains. Thus, for example, a mathematical model of the economy based on 100 variables "lives" in 100-dimensional space. So trying to visualize what goes on in such a space "is hardly just an exercise of the mind," Spencer says.

But it's not all bad news, the researchers say. The counterexamples that disprove the two conjectures are based on potentially useful properties of higher-dimensional space, properties that geometers simply aren't accustomed to. Higher-dimensional space "has a lot more flexibility and freedom of movement than is possible in lower-dimensional space," Lagarias notes. (By analogy, bridge played only with face cards is a mighty dull game.) That extra flexibility is a resource waiting to be tapped. In short, the new results might just open geometers' eyes to possibilities previously unimagined.

For the moment, though, the conjecture-quashing counterexamples are just mathematical eyebrow-raisers, with no immediate applications. Keller's conjecture is concerned with the problem of filling n-dimensional space with "cubes" of equal size, leaving no gaps and no overlaps. The "cubes" are higher-dimensional analogues of the two-dimensional square and the ordinary three-dimensional cube. In dimension two, it's easy to see that the no-gap/no-overlap requirement quickly forces at least two squares to be adjoined with an entire side in common. The same thing is true in dimension three (though it's harder to prove): Filling space with building blocks inevitably requires two of them to share an entire (square) side (see figure below).

In 1930, the German mathematician Ott-Heinrich Keller suggested this should continue to hold in higher dimensions. And it does hold for dimensions four, five, and six—Oskar Perron, also in Germany, proved that much in 1940. But Keller was wrong in general. Lagarias and Shor have found a way to fill 10-dimensional space with 10-dimensional cubes in such a way that none of them shares an entire (nine-dimensional) side with any neighbor.

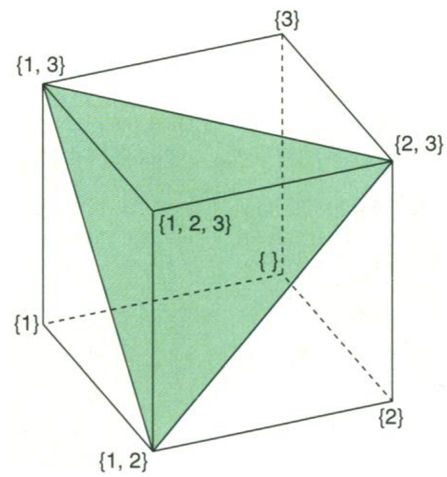
Since efforts to visualize the problem had led mathematicians astray in the first place, Lagarias and Shor didn't even try. Their construction, based on ideas introduced in 1990 by Kereszyély Corrádi at Eötvös University and Sándor Szábo at the Technical University in Budapest, is entirely algebraic. In essence, they specify an algebraic pattern for the numerical coordinates of the centers of their 10-dimensional cubes. This pattern guarantees that no two cubes share an entire side; Lagarias and Shor then verify that the arrangement leaves no gaps.



ILLUSTRATIONS BY D. DEFRANCESCO

Lagarias and Shor's 10-dimensional result can be parlayed into counterexamples in higher dimensions as well, but it leaves part of the problem unsolved: "We don't know whether Keller's conjecture is true in dimensions seven, eight, and nine or not," Lagarias notes. Those spaces may be flexible enough for counterexamples to exist, but they're not flexible enough for Lagarias and Shor's approach to work. In principle, a computer search through a finite number of possible ways of filling each space could settle the problem in dimensions seven, eight, and nine, Lagarias says, but the numbers are enormous. Even for n=7, this approach would require looking at up to 2^{128} possibilities—a number with enough digits to make a Cray blanch.

That fearsome prospect just goes to show how mathematicians can end up at sea when they can't rely on their intuition. Kahn and Kalai's effort to cut geometric figures down to size teaches the same lesson. The target of their research, Borsuk's conjecture, is concerned with how many pieces you need to chop an n-dimensional shape into in order to make the "diameter" of each piece less than the "diameter" of the original. Diameter, in this case, is the furthest distance possible between two points on the figure. That definition agrees with the ordinary meaning of diameter for circles and spheres, while for rectangles the diameter is the length of a diagonal, and for triangles it's the length of the longest side.



If you cut an equilateral triangle—whose diameter is the distance between any pair of vertices—into two pieces, then at least one of the pieces has the same diameter as the original, since one piece must contain two of the vertices. However, it is possible to cut the triangle into three pieces, each of smaller diameter. In 1933, the Polish mathematician Karl Borsuk proved that what goes for triangles is true for any figure in the plane: It can be cut into three pieces, each with diameter less than that of the original. He went on to speculate that three-dimensional figures can all be cut into four pieces of smaller diameter and, more generally, any n-dimensional shape can be cut into $n+1$ pieces of smaller diameter.

Although this speculation, which came to be called Borsuk's conjecture, was based on just one data point, it has an intrinsic intuitive appeal. At the very least, it's true for n-dimensional spheres, cubes, and tetrahedra: They can all be cut into $n+1$ pieces of smaller diameter. And in 1946, the Swiss mathematician Hugo Hadwiger proved the conjecture for all three-dimensional figures. But researchers still don't know whether or not every four-dimensional shape can be cut into five pieces of smaller diameter, or whether every five-dimensional shape can be cut into six pieces. In fact, the next several thousand cases of Borsuk's conjecture are still up in the air. The buck stops somewhere short of dimension 10,000, however. Kahn and Kalai have constructed a family of shapes—one for each dimension—which, at least for very high dimensions, require far more cutting than Borsuk had imagined.

Kahn and Kalai's shapes are n-dimensional polyhedra, each arranged within a cube of $n+1$ dimensions so that the vertices of the polyhedron fall at the corners of the cube (see figure at left). A subset of the integers 1 to $n+1$ is assigned to each corner of the cube, and the distance between corners is related to the number of integers the corresponding sets have in common (the farther, the fewer). That scheme, first proposed by David Larman at University College in London in 1984, turns Borsuk's conjecture into a purely combinatorial statement about the collections of integers.

Kahn and Kalai tailored their construction to make use of the combinatorial theory of finite sets. That theory, pioneered in the 1940s and 50s by the peripatetic mathematician Paul Erdös, has been extensively developed over the past several decades. Those developments gave Kahn and Kalai just what they needed: an estimate for the minimum number of pieces their shapes would have to be cut into. The estimate is dramatically different from Borsuk's conjectured $n+1$. Kahn and Kalai found that the number of pieces required for their n-dimensional shape is always greater than—get this!—$1.1^{\sqrt{n}}$.

For small values of n, that estimate is actually less than $n+1$, so it doesn't help solve the problem in those cases. But by around n=10,000, the exponential creeps above $n+1$. And as exponentials are wont to do, it quickly becomes much, much bigger than $n+1$. So Borsuk's conjecture isn't just wrong, notes Spencer, it's "very, very wrong."

For lower dimensions, though, Borsuk's conjecture may still hold. In particular, "dimension four is wide open," says Kalai. Kalai, for one, is leery of trying to predict which way it might go, except to say that current approaches won't provide the answer. "You clearly need a different way to look at the entire problem" in four dimensions, he says. One dimension removed from the familiar world, it seems, is more than enough to frustrate mathematical intuition.

–Barry Cipra